REMARKS/ARGUMENTS

The present amendment is submitted in accordance with the *Revised Amendment Format* as set forth in the Notice provided on the USPTO web site for the Office of Patent Legal Administration; Pre-OG Notices; signed 1/31/03.

Claims 1-51 are pending in the application. Claims 1-14 are examined on the merits. No claims are allowed. Claims 15-51 have been canceled without prejudice to subsequent revival. Applicants reserve the right to prosecute claims 15-51 in a divisional application.

Claims 1 and 12-14 have been amended. Claims 3, 5, 6, 9 and 11 have been canceled. Entry of the amendment, reconsideration of the rejection, and allowance of claims 1, 2, 4, 7-8 and 12-14 are requested.

The Amendment

In order to expedite prosecution of the application and advance the case toward allowance, the claims have been amended. No new matter was introduced by this amendment.

Claim 1 has been amended to specify that the method of producing complete Hepatitis A Virus (HAV) particles includes the steps of "providing a cell culture supernatant of an HAV infected VERO cell culture; concentrating the cell culture supernatant"; treating an HAV preparation from the cell culture supernatant of the HAV infected cell culture with a nucleic acid degrading agent and a protease; "filtering to remove impurities to obtain a purified preparation of complete HAV particles in a single step"; and isolating said purified preparation of complete HAV particles. Support for this amendment can be found on page 13, paragraph [051], lines 3-4; page 11, paragraph [043], lines 2-3; page 13, paragraph [048], line 6; and page 13, paragraph [049], lines 1-2.

Claims 12 and 13 have been amended to specify that the preparation of complete HAV particles is "purified". Support for this amendment can be found on page 13, paragraph [048], line 7.

Claims 13 and 14 have been amended to correct a spelling error, wherein "particle" was changed to "particles".

Rejection Under 35 U.S.C. §112

Claims 1-14 have been rejected under 35 U.S.C. §112, second paragraph, as being allegedly incomplete for omitting essential steps.

Herein, the Examiner requests clarification to how the HAV preparation is made in claim 1. The Examiner also requires clarification on how many filtering steps are involved in claims 1 and 11.

To the extent that the rejection applies to the claims a amended, the rejection is respectfully traversed.

Claim 11 has been canceled. Claim 1 has been amended to comply with the Examiner's suggestion and clarify how the HAV preparation is made and how many filtering steps are involved. As such, the claim has been amended to specify that the method comprises the steps of providing a cell culture supernatant of an HAV infected VERO cell culture; concentrating the cell culture supernatant; treating an HAV preparation from the cell culture supernatant of the HAV infected cell culture with a nucleic acid degrading agent and a protease; filtering to remove impurities to obtain a purified preparation of complete HAV particles in a single step; and isolating the purified preparation of complete HAV particles. All other pending claims depend on claim 1. The invention requires only one filtering step which results in an HAV purity of 98% or greater (see page 10 of the specification, paragraph [039]). Optionally, the cell culture supernatant in step 2 may be concentrated via ultrafiltration. However, other methods, such as centrifugation, precipitation, or 2-phase partitioning may also be used (see page 11 of the specification, paragraph [043]).

In light of this amendment, Applicants respectfully request that the rejection of claims 1, 2, 4, 7-8, 10 and 12-14 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 5 and 6 are rejected under 35 U.S.C. §112, first paragraph, for being allegedly not enabling for producing the same high yield of HAV particles by using any other microbial protease as claimed in claims 6 and 7.

In the interest of prosecution efficiency, claims 6 and 7 have been canceled. Hence, this rejection should be moot. However, this amendment is made to advance the claims toward allowance and must not be construed as an acquiescence in the rejection.

Rejection Under 35 U.S.C. §102

Claims 1-5 and 11 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Robertson. *et al.* (USPN 5,268,292A). Furthermore, claims 1-2, 4-5 and 14 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Kuzuhara *et al.* (EP 0 339 667B1).

Herein, the Examiner alleges that the physical isolation processes of HAV particles taught by Robertson *et al.* mainly involve filtration which meets the limitations of claims 3 and 11 and because trypsin (with which the particles are treated) is a protease, it meets the limitation of claim 2. The Examiner also asserts that Kuzuhara *et al.* anticipate the claimed invention because they teach a method of isolating HAV particles with the steps of harvesting the particles from the cells by centrifugation; treating the particles with DNase 1 and Proteinase K; concentrating the particles by centrifugation; purifying the particles by gel filtration; sterilizing the positive fraction by filtration; and inactivating the purified virus with formalin.

The rejection is respectfully traversed to the extent that the rejection applies to the claims as amended.

"In order for a rejection under §102(b) to be valid, each and every element of the claim must be found in the prior art reference." (MPEP 2131; *In re Royka and Martin,* 180 USPQ 580 (CCPA 1974)).

The amended claims are directed to a method of producing complete Hepatitis A Virus (HAV) particles with the steps of providing a cell culture supernatant of an HAV infected *VERO cell culture*; concentrating the cell culture supernatant; treating an HAV preparation from the cell culture supernatant of the HAV infected cell culture with a nucleic acid degrading agent and a protease; *filtering* to remove impurities to obtain a purified preparation of complete HAV particles *in a single step*; and isolating the purified preparation of complete HAV particles.

In comparison, neither Robertson *et al.* nor Kuzuhara *et al.* teach a method of producing complete HAV particles in VERO cells. Robertson employs a fetal rhesus monkey kidney cell line (FRhK4 cells) (see column 8, line 65) and Kuzuhara employs GL-37 cells, derived from African Green monkey kidney cells (see page 4, line 41). Clearly, the early work of Robertson and Kuzuhara was inclusive of the shortcomings these cells impose when used in conjunction with HAV production, specifically for the purpose of vaccine preparations. As stated in the background of the specification on page 1, paragraph [003], HAV is the only hepatotropic virus which can be isolated from cell culture, but the virus is usually difficult to propagate, with long incubation periods and no cytopathic effect. Even though several primate cell types have been reported to support replication of HAV, such as a fetal rhesus monkey kidney cell line (FRhk-4), primary African green monkey kidney cells (AGKM), and continuous African green monkey kidney cells (BCS-1), these cannot generally be used for human vaccine because monkey kidneys often have a high content of latent simian viruses which become apparent in the course of virus production for vaccine.

The background of the specification also discusses that all strains of HAV which have been grown in cell culture are characterized by inefficient release of virus into the culture supernatant. Although as much as 50% of infectious virus may be released, typically less than 30% of infectious virus is extracellular (see page 3 of the specification, paragraph [009]). Because HAV antigen is not efficiently released into the culture supernatant and methods to concentrate the large volume are costly, most purification processes described use HAV antigen from cell lysate of intracellularly produced virus as source for production of HAV vaccine (**EP 0339 667, Kuzuhara *et al.***). However, these processes are time-consuming, make use of detergent necessary to release intracellularly produced antigen from the cells and **need intense and serial purification steps** to remove detergent and contaminants derived from the cells. Hence, such HAV large scale preparations from cell lysates and/or cell culture supernatants contain mixed populations of mature virions, provirions and procapsids (**EP 0339 667, Kuzuhara *et al.***) (see page 4 of the specification, paragraph [009]).

Furthermore, neither Robertson *et al.* nor Kuzuhara *et al.* teach a method of producing complete HAV particles in VERO cells, wherein filtering is employed to remove

impurities to obtain a purified preparation of complete HAV particles *in a single step*. Robertson *et al.* teach that media was concentrated by ultrafiltration, precipitation, and centrifugation (see column 5, lines 40-50). Then, fractions of HAV antigen grown in FRhk-4 cells were pooled, concentrated and dialyzed into TN buffer using a Centriflo cone. The concentrated pool was then layered in sucrose gradient and centrifuged. Fractions were collected, pooled, concentrated and again dialyzed using a Centriflo cone (see column 6, lines 17-27). From this description it is clear that Roberton *et al.* does not obtain purified HAV particles after a single filtering step. In fact, Robertson *et al.* teach three filtering steps. Kuzuhara *et al.* rely on a method of HAV production, wherein HAV antigen is derived from cell lysate of intracellularly produced virus (*supra*) and serial purification steps are required to remove detergent and contaminants derived from the cells (see page 4, lines 55-58 and page 5, lines 1-19). Thus, neither Robertson *et al.* nor Kuzuhara *et al.* anticipate the claimed invention.

In light of the amendment and arguments presented above, Applicants respectfully request that the rejection of claims 1-5, 11 and 14 under 35 U.S.C. §102(b), be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 1-5, 9-11 and 14 are rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Robertson. *et al.* (USPN 5,268,292A), Provost *et al.* (USPN 4,783,407), Kistner *et al.* (WO 96/15231A2), Cinatl Jr. *et al.* (Biology International 1993, Vol. 17, No. 9, pp. 885-895) and Kuzuhara *et al.* (EP 0 339 667B1).

The Office Action alleges that one would have been motivated by the cited references to generate the purified HAV particles by combining all well established methods in the art as described and that the invention as a whole is *prima facie* obvious in the absence of unexpected results.

The rejection is respectfully traversed to the extent that the rejection applies to the claims as amended.

As the Examiner is aware, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). However, in

this case the prior art references do not teach or suggest all the limitations of the claims and therefore, the obviousness rejection should be withdrawn.

As discussed above, neither Robertson *et al.* nor Kuzuhara *et al.* teach a method of producing complete HAV particles in VERO cells, ***wherein filtering is employed to remove impurities to obtain a purified preparation of complete HAV particles in a single step***. The other three references cited by the Examiner do not discuss this limitation either. In fact, the Examiner has pointed to nothing in the secondary references that teaches or suggests this element of the claimed method. Since in each case, all of the claim limitations are not suggested by the combination of references, the rejection should be withdrawn.

As the Examiner is further aware, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As shown above, neither Robertson *et al.* nor Kuzuhara *et al.* anticipate the claimed invention. Thus, Robertson's or Kuzuhara's disclosure coupled with the knowledge of deriving HAV in VERO cells from homogenized cell culture (see Provost *et al.*, column 4, lines 6-7) and/or the knowledge that influenza virus can be produced by utilizing vertebrate cells cultured under protein-free conditions, wherein the virus found in the cells is released by lysis (see Kistner *et al.*, page 31, lines 17-18) and/or the knowledge that a protein free media was developed for VERO cells on a PVF culture surface for the propagation of viral titers of coxsackievirus B4, herpes simplex virus, measles virus, and polio virus (see Cinatl Jr. *et al.*, abstract and page 887, column 1) does not teach the skilled artisan to produce the claimed invention. There is simply no motivation to combine the references because applying Robertson's or Kuzuhara's method to any or all of the methods taught by Provost, Kistner and/or Cinatl would not lead to the claimed method.

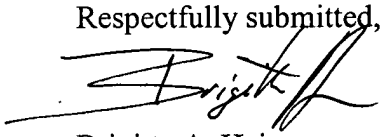
In light of the amendment an arguments presented above, Applicants respectfully request that the rejection of claims 1-5, 10-11 and 14 under 35 U.S.C. §103(a), be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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